## REMARKS

With this amendment, claims 70-99 stand presented. Claims 70-84 remain as presented in the previous amendment mailed December 1, 2003, with the exception of a typographical correction to claim 84 to add a period punctuation mark at the end of the claim.

New claims 85-99 are added by the present amendment. While support in the specification and in the originally submitted claims for these new claims is now summarized, the full text of these new claims should be consulted for a complete understanding of the subject matter presented by the claims.

New dependent claim 85 specifies that the nitric oxide gas of claim 79 is diluted with an oxygen containing gas, and finds support in the specification at, for example, page 8, ll. 10-19.

New independent claim 86 recites a method for treating an animal having pathogenic microorganisms in the respiratory tract of the animal, comprising the step of delivering by the inhalation route to the respiratory tract of the animal an amount of nitric oxide gas effective to kill or inhibit the proliferation of said pathogenic microorganisms. This claim finds support in, for example, originally presented claims 14 and 15 (methods for treating pathogenic cells or microorganisms) and in the specification at, for example, page 5, line 31 to page 6, line 3 (same) and page 6, line 31 to page 7, line 3 (cidal and inhibitory effects described).

New claims 87-99 all depend directly or indirectly from claim 86. The limitations of these dependent claims are broadly patterned after originally presented claims 16-18 and 20-29, respectively, and find support in these originally presented claims and in the disclosures in the specification corresponding to these claims.

Favorable consideration of these newly presented claims, and reconsideration of the rejection of previously presented claims 70-84, are respectfully requested.

**A. The Obviousness Rejection Should Be Reconsidered and Withdrawn**

Previously presented claims 70-84 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Green et al. (WO 95/09612) in view of Bathe et al. (U.S. Patent No. 5,558,083). This rejection is respectfully traversed. For reasons explained in more detail below, the cited references do not teach or suggest the use of inhaled nitric oxide **gas** – as distinct from nitric oxide "generating" compounds, which are not nitric oxide gas – to kill or inhibit the proliferation of pathogens in the respiratory tract of an animal. To the contrary, Green directly teaches against the use of nitric oxide gas, as being (for example) overly reactive, poorly soluble, and difficult to administer reliably (e.g., page 4, ll. 12-18).

In support of the present arguments in favor of the allowability of the present claims over the cited references, applicant submits herewith a declaration under 37 C.F.R. § 1.132 from Dr. Neil MacIntyre, M.D. As will be seen from the declaration and his C.V., Dr. MacIntyre is a prolific researcher and practicing medical expert in the field of respiratory care. Among his many scientific publications in the field, Dr. MacIntyre has written extensively on the use of "*aerosols*" for respiratory administration (aerosols being the only "inhaled" form of therapy mentioned in the Green reference) and also on the use of inhaled *gases* as presently claimed. In the opinion of Dr. MacIntyre, the cited references (including Green) do not teach the presently claimed invention, and do not render the claimed invention obvious.

1. The Present Claims Are Directed to Inhalation of Nitric Oxide **Gas**

As a preliminary matter, applicant wishes to make clear that the present claims (both claims 70-84 as previously presented and new claims 85-99) are limited to the inhalation of nitric oxide **gas**. The claims are not addressed to the inhalation of other compounds that may, at some point after inhalation, "generate" or otherwise release nitric oxide (NO). In this regard, the

Examiner stated at page 5 of the April 16, 2004 Office Action that "the instant claims do not require a delivery of nitric oxide gas directly to the respiratory system." Applicant respectfully submits that this is not correct. Specifically:

Independent claim 70 calls for "a flow-controlled source of nitric oxide **gas**," for "delivering the nitric oxide **gas** to the animal's respiratory tract through inhalation," and for "inhalation of nitric oxide **gas**";

Independent claim 79 calls for "providing a pressurized source of nitric oxide **gas**," for "diluting the nitric oxide **gas**," and for "delivering the nitric oxide **gas** to the animal by inhalation";

New independent claim 86 calls for "delivering by the inhalation route to the respiratory tract of the animal an amount of nitric oxide **gas** ...".

Thus, applicant submits that it is abundantly clear that the claims do indeed require "delivery of nitric oxide gas directly to the respiratory system." This remains true, and is consistent with, the language in claims 70 and 79 reciting a "**source** of nitric oxide **gas**," and the language in claim 76 reciting "a nitric oxide **substrate source** containing a compound capable of producing nitric oxide **gas**." Whether the original "source" of the nitric oxide gas is (for example) a pressurized tank containing nitric oxide gas (molecular NO in gaseous form), or a "substrate source" that is capable of producing nitric oxide gas, or some other "source" of nitric oxide gas, the fact remains that it is nitric oxide **gas** that is inhaled by the animal according to all the claims. What is inhaled, according to all the claims, is not some other chemical entity that might (as in Green), at some point after inhalation, "generate" or otherwise release nitric oxide through chemical transformation, enzymatic action or some other mechanism. This is one central feature that distinguishes the present invention from the teachings of the Green reference.

2. Green Does Not Teach or Suggest the Use of Inhaled Nitric Oxide Gas

The Green reference does not disclose the inhalation of nitric oxide gas for killing, inhibiting or suppressing pathogenic microorganisms, as claimed by applicant. Instead, as the Office Action recognizes, Green only "teaches *compositions capable of releasing nitric oxide* and therapeutic methods of use thereof for the treatment of microorganism-related disease states." April 16, 2004 Office Action, p. 2 (emphasis added).

Although the Office Action states that Green "discloses that direct delivery of nitric oxide gas kills intracellular pathogens such as *Mycobacterium tuberculosis*," this statement in Green clearly does not teach the delivery of gaseous nitric oxide through inhalation. First, the cited sentence in Green does not refer to the direct delivery (let alone inhalation) of nitric oxide gas at all, but rather to the direct delivery of "nitric oxide" to the intracellular environment. Furthermore, Green in this context is describing the generation of nitric oxide from some precursor compound via enzymatic reaction or some other "releasing" mechanism:

> Nitric oxide gas can be formed metabolically from the amino acid L-arginine through the action of the enzyme nitric oxide synthase. Recent evidence shows that direct delivery of nitric oxide kills intracellular pathogens such as *Mycobacterium tuberculosis.* An ability to specifically deliver compounds capable of releasing nitric oxide to the desired site of infection within the macrophage would greatly enhance killing of intracellular pathogens.

Green, p. 5, ll. 6-13 (underlining added).

As seen from the last sentence of quoted paragraph, and from the entirety of the Green disclosure and claims, one of ordinary skill in the art cannot but conclude that Green's disclosure is directed toward delivery of specialized compounds other than nitric oxide gas – namely "compounds which *release* nitric oxide in *aqueous solution*" (Green, p. 1, ll. 15-17, emphasis added) – rather than delivery of nitric oxide gas itself through inhalation.

For example, in its "Summary of the Invention" section, Green states that "the present invention involves exposing cells to a compound capable of *releasing* nitric oxide *in an aqueous solution,* particularly a *nitric oxide/nucleophile complex* or derivative thereof." Green, p. 7, ll. 16-20 (emphasis added).[1] Additionally and specifically with respect to the respiratory system, Green teaches that one might "aerosolize *closed membranous vesicles* containing nitric oxide *generators* for administration to the respiratory system through inhalation." p. 8, ll. 21-23.[2] Nowhere does Green teach the delivery of *gaseous* nitric oxide through inhalation for inhibiting, killing, or suppressing pathogenic microorganisms, let alone the step of "providing a flow-controlled source of nitric oxide gas" (claim 70), or "providing a pressurized source of nitric oxide gas" (claim 79), or "delivering by the inhalation route to the respiratory tract ... an amount of nitric oxide gas ..." (new claim 86).

To the contrary, Green directly teaches away from the use of inhaled nitric oxide gas. According to Green, "[n]itric oxide in its pure form ... is a highly reactive gas having limited solubility in aqueous media ... [and], therefore, is difficult to introduce reliably into most biological systems without premature decomposition." Green, p. 4, ll. 13-18. Hence, Green

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[1] *See also, e.g.,* p.1, ll. 15-19 ("the present invention is directed to the use of compounds which release nitric oxide in aqueous solutions ..."); p. 8, ll. 12-13 ("object of the invention is to use liposomes containing nitric oxide generators to treat macrophage-based diseases caused by viruses, bacteria, parasites, and fungi."), p. 9, ll. 23-28 ("The present invention is predicated on the discovery that cell proliferation can be attenuated or inhibited by exposing cells to a compound that is capable of releasing nitric oxide in an aqueous solution ...."); p. 3, ll. 17-20; 32-33 ("release nitric oxide in aqueous solution."); p. 4, l. 6 ("nitric oxide solutions..."); p. 6, ll. 5-8 (distinguishing prior art and stating that prior art does not disclose "a preparation of *liposomes* that contain nitric oxide *generators* ....") (emphasis added); p. 41, claim 1 ("a compound capable of releasing nitric oxide in an aqueous solution").

[2] *See also, e.g.*, p. 23, ll.7-10 ("The nitric oxide releasing compounds in the context of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation."); p.27, ll. 35 ("Liposomes are a desirable vehicle for administering nitric oxide generators ...."); p. 29, ll. 14-25 ("Nitric oxide generator-containing vesicles are administered via ... inhalation ...")

teaches that "[t]he use of [non-gaseous compounds capable of releasing nitric oxide in aqueous solution] in treating animals, particularly humans, circumvents the *disadvantages* of the use of *pure nitric oxide* ...." Green, p. 21, line 35 to 22, line 1.

3. The Accompanying Expert Evidence Supports a Conclusion of Non-Obviousness

The accompanying Rule 132 declaration of Dr. Neil MacIntyre ("MacIntyre Declaration") amply supports the conclusion that the Green reference does not teach or suggest the claimed invention, and even in combination with other art relating to the administration of gaseous nitric oxide (such as the cited Bathe reference) does not render the claimed invention obvious.

As indicated in paragraph 2 of the MacIntyre Declaration and in his accompanying C.V., Dr. MacIntyre is a tenured Professor of Medicine at Duke University Medical Center, where he is also Chief of Clinical Services for pulmonary and critical care medicine, and Medical Director of Respiratory Care Services. He has had over 25 years of professional experience specializing in respiratory care and pulmonary disease medicine. He has authored or served as editor of hundreds of publications in this field.

Dr. MacIntyre has studied the Green reference and concludes that Green does not disclose the use of inhaled nitric oxide gas to kill or inhibit microorganisms in the respiratory tract, and does not render obvious the use of nitric oxide gas for these purposes. MacIntyre Declaration, e.g., ¶¶ 3, 17. As pointed out in the remarks above, the Green reference discloses only the use of nitric oxide "generators" or "releasing compounds," which in Dr. MacIntyre's opinion are very different from nitric oxide gas. E.g., ¶¶ 4, 7, 14-15. Moreover, Dr. MacIntyre agrees that Green in fact teaches away from the approach of delivering nitric oxide gas directly through inhalation for killing or inhibiting microorganisms in the respiratory tract. ¶¶ 5-6.

Dr. MacIntyre explains in his declaration that all of the compounds and methods taught by Green involve the use of large, compound molecules that simply cannot be administered in gaseous form. E.g., ¶¶ 4, 8. These compounds include non-gaseous "nitric oxide/nucleophile" adducts, as well as even larger components that can include polymer materials, liposomal vesicles, targeting antibodies, and other materials that clearly do not lend themselves to a gaseous state. E.g., ¶ 4, 7.

Dr. MacIntyre also describes some of the significant clinical differences that arise in the administration of, on the one hand, the ***aerosol*** formulations required to deliver the non-gaseous compositions described by Green and, on the other hand, nitric oxide ***gas*** as claimed in the present applications. Dr. MacIntyre has worked extensively in clinical applications using both aerosol and gas forms of inhaled therapeutic compositions (see, e.g., ¶¶ 9, 2), and is highly qualified to speak to these issues.

In this regard, the Examiner has correctly observed that Green refers to the administration of the described nitric oxide releasing compounds using "aerosol" formulations that contain the releasing compound. April 16, 2004 Office Action, p. 3; Green, p. 23, ll. 7-13; p. 29, ll. 15-25. The described use of aerosols to administer a non-gaseous active agent is fundamentally different from the administration of gaseous nitric oxide. MacIntyre Declaration, ¶ 8. For example, even with the best techniques, standard aerosolization devices are able to deliver only a limited amount of their aerosol material into the lungs, and the dose delivered will vary from patient to patient and from device to device. ¶¶ 11-12. Furthermore, there is a significant potential that only a relatively small portion of the volume of the lung (perhaps on the order of 20 percent) will be reached by an aerosol material, which would result in significantly different doses of the non-gaseous active agent reaching different regions of the lung. ¶ 13. This latter shortcoming leads

to the additional risk that, because some regions will be under-treated while others may be overdosed, pathogen mutagenicity and potential development of drug-resistant pathogens may occur. ¶¶ 10, 13.

The administration of inhaled nitric oxide ***gas***, as claimed in the present application, offers significant advantages over the non–gaseous aerosol formulations taught by Green. Gaseous nitric oxide can be breathed continuously and will very rapidly (usually within 3-7 minutes) reach a steady state condition in which all surfaces of the lungs that are in communication with the airways would be exposed to a uniform concentration of the drug. MacIntyre Declaration, ¶ 14.

Conversely, if it is desired to change the concentration of the delivered nitric oxide gas, or to terminate treatment altogether for some reason, this can be easily accomplished with nitric oxide gas simply by altering the concentration of nitric oxide in the inhaled ventilatory gas or by ceasing delivery of the drug. The effect of inhaled nitric oxide gas generally lasts less than about six seconds, so changes in dosing and in physiological effect can be very rapidly accomplished. ¶ 15. This stands in stark contrast to the non-gaseous, aerosolized compounds taught by Green, which will remain in place in the lung tissue until naturally absorbed or deactivated, or until a second "scavenger" compound is administered to "counteract the inhibitory effect of the compound capable of releasing nitric oxide." See Green, p, 21, ll. 17-26. Even so, the administration of such a "scavenger" compound would still suffer from the same drawbacks of inconsistent and incomplete delivery regions, variable dosages, and unpredictable effects as associated with the original "nitric oxide generator" aerosol formulation. MacIntyre Declaration, ¶ 16.

Thus, there are numerous bases for distinguishing the approach claimed in the present application from that described by Green. As Dr. MacIntyre explains, these include the fact that inhaled nitric oxide gas does not suffer from several drawbacks of the non-gaseous aerosol approach of Green, and offers significant advantages such as consistency of dosing, maximization of the regions of application in the lung, and the ability to change or even cease administration virtually instantaneously.

For such reasons, it is Dr. MacIntyre's opinion that the invention of the present application would not have been obvious in view of the Green reference and other art (such as Bathe) teaching other applications for inhaled nitric oxide gas. This conclusion stands particularly strong in light of the cautions against the use of nitric oxide gas expressed by Green, which were unrelated to the ability to inhale nitric oxide gas but related, rather, to Green's view that the gaseous form of molecular nitric oxide lacked potential effectiveness against respiratory pathogens. See MacIntyre Declaration, ¶ 17.

**B. Conclusion**

For the foregoing reasons, applicant respectfully submits that Green and the other cited art do not render obvious applicant's previously presented independent claims 70 and 79, nor their respective dependent claims. For the same reasons, newly submitted claims 86-99 are patentable over the art of record, and their consideration and allowance is respectfully requested.

Applicant believes that the claims of this application are patentable and respectfully requests the issuance of a Notice of Allowance. If the undersigned can be of any assistance to the Patent Office, a telephone call is respectfully requested.

Respectfully Submitted

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